Quiz #50
Ketamine in Neuroanesthesia

This Quiz is being published on behalf of the education committee of SNACC.

M. Angele Theard, MD, Legacy Emanuel Medical Center, Portland, OR
Quiz Team: Shobana Rajan MD, Suneeta Gollapudy MD, Verghese Cherian MD
1. Which of the following is true regarding recommended uses of Ketamine?

A. As an induction agent for patients with eye injury.
B. As an analgesic in patients who have been diagnosed with schizophrenia.
C. For analgesia in patients with chronic pain and acute postoperative pain.
D. As an anesthetic for elective surgery in children <4 years of age.
A. As an induction agent for patients with eye injury.

This is not true. Ketamine as an induction agent (0.5-2 mg/kg IV) is beneficial in the unstable trauma patient. This drug’s cardiovascular stimulant effects derived from the systemic release of catecholamines and inhibition of norepinephrine reuptake at peripheral nerves leads to increases in BP, HR, and CO. However, in patients with an open eye injury, Ketamine-induced increase in IOP maybe disastrous.

Additionally, caution is recommended in the hemodynamically stressed patients as the direct cardiac depressive action of ketamine may be unmasked causing cardiovascular collapse.

B. As an analgesic in patients who have been diagnosed with schizophrenia

This is not true. Ketamine administration as a single bolus dose (0.3 mg/kg) has been shown to exacerbate psychotic symptoms in patients suffering from schizophrenia. Similarly, Malhotra et al. also reported that ketamine as an i.v. bolus of 0.12 mg/kg, followed by a 60-minute infusion of 0.65 mg/kg increased psychotic symptoms in patients suffering from schizophrenia.

C. For analgesia in patients with chronic pain and acute postoperative pain

This is true. Ketamine modulates pain at the dorsal horn of the spinal cord. This phencyclidine derivative is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. Ketamine appears to be beneficial in reducing opioid consumption associated with delayed rehabilitation and poor outcomes in patients for lumbar spine surgery. In a randomized, prospective double blinded and placebo-controlled trial involving opiate-dependent patients undergoing major lumbar spine surgery, patients who received 0.5mg/kg IV ketamine followed by an infusion of 10mcg/kg/min as part of a balanced anesthetic technique together with their normal daily dose of opiates demonstrated a significantly reduced morphine consumption at 48 hours after the procedure compared to placebo.

Pasternak J, JNA, 2019;31(2):178-98
D. As an anesthetic for elective surgery in children <4 years of age.

This is not true. Current recommendations support avoiding ketamine for repeated nonurgent surgeries for children < 4 years.

Ketamine’s ability to cause damage in the developing brain of animals raises concern for its use in young children. Blockade of NMDA receptors whose activation is essential for long term potentiation of the hippocampus, spatial learning and memory and upregulation of NMDA receptors with consequent increased susceptibility to the excitotoxic effects of endogenous glutamate are two explanations for Ketamine’s role in impaired neurodevelopment. Ketamine has also been demonstrated to inhibit neuronal stem progenitor cells (NSPC) proliferation and enhance NSPC differentiation in rat neocortex. Using human neural stem cell culture, Bai et al found that ketamine causes significant neuroapoptosis after 24 hours exposure.

In retrospective human studies, however, ketamine used in several emergency departments (low doses for sedation or analgesia) in close to 10,000 children revealed no adverse neurological sequelae, although long-term neurodevelopment follow-up is missing from this data.

Davidson A. Pedatire Anesthesia, 2010;1:716-21
2. A 45 year old 65 Kg female with chronic lower back pain on daily opiates for 3 months presents for a L1-3 lumbar fusion. Preoperatively, the patient received 150 mg pregabalin and a scopolamine patch and intraoperatively received ketamine, Propofol, Lidocaine and fentanyl. Lacrimal ointment was applied together with tape for ocular occlusion. The Patient was hemodynamically stable during surgery which lasted 3 hours. Blood loss was 200 cc and the patient received 2 L crystalloid and 250cc of colloid. In the PACU, the patient complains of blurry vision. All of the following are possible reasons for this patient’s visual changes EXCEPT:

A. Ketamine
B. Ischemic Optic Neuropathy
C. Propofol
D. Pregabalin

Go to Q 3
This is true. Ketamine, available in the US as a racemic mixture of enantiomers (S) and (R) enantiomers is a useful analgesic for opioid tolerant patients like this undergoing spine surgery. Nystagmus, a side effect of Ketamine causes involuntary repetitive eye movements causing blurred vision which compromise a patient’s ability to focus. The more potent (S) enantiomer appears to carry a higher predilection for this side effect. 100% of Patients with orofacial pain treated with (S) Ketamine had blurred vision compared to 85% treated with (R,S) Ketamine and 78% treated with (R) Ketamine.
B. Ischemic Optic Neuropathy

This is true. Postoperative visual loss (POVL) which may manifest initially as blurred vision occurs in 0.2% of spine surgeries and 4.5% of cardiac surgeries. Most of these cases are due to Ischemic optic neuropathy (ION) with rare cases due to retinal ischemia and cortical blindness. Observation in the PACU for continued improvement is reassuring in this female patient who is not obese and received colloid intraoperatively. As this symptom can be indicative of potential permanent visual loss, close observation in the PACU together with a formal ophthalmic evaluation if this visual change does not improve is warranted.


### Risk Factors for ION

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Male Sex</td>
</tr>
<tr>
<td>Wilson Frame use</td>
</tr>
<tr>
<td>Long anesthetic duration</td>
</tr>
<tr>
<td>Greater estimated blood loss</td>
</tr>
<tr>
<td>Decreased percent colloid administration</td>
</tr>
</tbody>
</table>
C. Propofol

This is not true. In a retrospective evaluation of 39,431 patients undergoing non-ocular surgeries, ocular findings were reported in 9 cases. General anesthesia with Propofol and remifentanil was used in 5 patients who complained of pain and photophobia but no blurred vision. Four patients who received a balanced general anesthetic complained of pain with one patient reporting blurred vision. The most common diagnostic sign noted in these patients was hyperemia due to trauma or dry eyes.

In a prospective study by Warner et al, 4.2% (28/671) of patients undergoing general anesthesia or regional anesthesia reported new onset of blurred vision lasting at least 3 days after surgery. Seven of the 28 patients required new corrective lenses or changes in their prescription. No risk factors were identified. While transient blurring of vision is often associated with intraoperative use of ocular ointments (used in this patient), excessive drying of the cornea or corneal trauma, other etiologies include decreased accommodation due to increased age and dysfunction of ciliary muscle due to trauma. While the anesthetic in this study was not standardized, anesthetic agents were not found to be a significant risk factor in this group.


Warner et al, Perioperative visual changes. Anesthesiology, 2002;96:855-9
D. Pregabalin

This is true. In clinical trials, blurred vision is reported by 6.4% of patients. Other more commonly reported side effects include somnolence (29.2%) and dizziness (22.2%). These effects are usually transient. Pregabalin (Lyrica), a synthetic molecule (GABA analog) which possesses anticonvulsant and anxiolytic actions, has been shown to be beneficial in patients undergoing elective spinal fusion surgery. Patients who received celecoxib 200mg and pregabalin 150mg preoperatively had significantly reduced pain and opioid use postoperatively.

3. Undesirable effects of ketamine administration include all of the following EXCEPT:

A. Hallucinations  
B. Decreased concentration  
C. Urological complications  
D. Increased amplitude in SSEP and MEP monitoring during spine surgery

Go to Q 4
A. Hallucinations

This is true. Hallucinations, unusual thought content, and suspiciousness are some positive psychotomimetic effects caused by subanesthetic doses of ketamine. Additional negative reactions include delirium, nightmares, and alterations in short term memory and cognition.

In a randomized, double-blind, placebo-controlled study, a 40 minute IV infusion of Ketamine (0.5mg/kg) lead to positive and negative psychotomimetic symptoms within 10 minutes of starting the infusion and subsided within 40 minutes of treatment end. At a dose of 0.1mg/kg, little to no psychoactive effects were observed.

Benzodiazepines seem to be the most effective drugs used for reducing the incidence and severity of these reactions.


B. Decreased concentration

This is true. Ketamine decreases concentration at subanesthetic doses. (0.5mg/kg IV bolus / 40-120 min IV infusion of 0.4-0.8mg/kg). However, global cognitive function and immediate recall remain intact.

C. Urological complications

This is true. Dysuria, increased frequency, incontinence, and hematuria can occur with prolonged recreational use of ketamine. CT reveals marked bladder wall thickening and mucosal enhancement associated with ketamine use.

In one case report, these complications were observed with a Ketamine dose of 0.1mg/kg/hour IV for 12 hours.

D. Increased amplitude in SSEP and MEP monitoring during spine surgery

This is not true. Ketamine is a desirable agent for use during spine surgery with neuromonitoring. While volatile anesthetics produce an increase in latency and decrease in amplitude of cortical sensory responses, Ketamine increases cortical SSEP amplitude and the Compound muscle action potentials (CMAPs) response of MEP. The increased myocardial work from ketamine-induced catecholamine release may not be desirable in some patients with cardiac disease.

Suebert Christoph, Mabla M, Neurologic Monitoring, In Miller’s anesthesia, ed. Miller et al, 8th ed. 2015 Elsevier Saunders, PA

4. All of the following statements are true regarding Ketamine administration EXCEPT:

A. Ketamine may prevent opioid-induced hyperalgesia
B. Ketamine has been used safely in patients with intracranial pathology under appropriate conditions
C. Better hemodynamic stability and improved sedation are achieved when ketamine is added to Dexmedetomidine for sedation for fiberoptic intubation
D. This drug is not effective for the treatment of bronchospasm
A. Ketamine may prevent opioid-induced hyperalgesia

This is true. NMDA receptor stimulation plays a role in inducing hyperalgesia after opioids in animals. Prophylactic ketamine administration therefore may help prevent central sensitization and long-lasting enhancement in pain sensitivity induced by opioid administration. These effects contribute to ketamine’s effectiveness as part of a multimodal approach for chronic pain.


B. Ketamine has been used safely under appropriate conditions in patients with intracranial pathology

This is true. Ketamine at doses 1.5, 3, or 5 mg/kg significantly decreased ICP in mechanically ventilated patients (PaCO₂ 35-38mmHg) with TBI during propofol anesthesia. No differences in CPP, jugular venous bulb O₂ saturation and middle cerebral artery blood flow velocity were observed between ketamine and placebo. Additionally, there is some developing evidence to support a neuroprotective influence of Ketamine through its NMDA-receptor activation, anti-inflammatory actions and attenuation of neuronal hyperexcitability.


Albanese J, Arnaud S, et al, Anesthesiology, 1997;87:1328-34
C. Better hemodynamic stability and improved sedation are achieved when ketamine is added to Dexmedetomidine for sedation for fiberoptic intubation.

This is true. In a randomized, double blinded study of 60 patients, the use of dexmedetomidine plus ketamine combination in awake fiberoptic nasotracheal intubation provided better hemodynamic stability and sedation than dexmedetomidine alone. The authors suggested that ketamine’s catecholamine-induced cardiovascular stimulant effect balanced the opposing action of Dexmedetomidine on the cardiovascular system.

D. This drug is not effective for the treatment of bronchospasm.

This is not true. As a sympathomimetic, ketamine serves as an effective bronchodilator useful in the treatment of patients with bronchospasm. Consideration of treatment with an antisialagogue to counteract the increased salivation from ketamine administration may provide additional benefit, particularly in children.

5. All of the following are pharmacokinetic properties of Ketamine EXCEPT

A. Metabolism by the liver
B. High lipid solubility
C. Elimination half life of 2-3 hours
D. The bioavailability of the Intranasal route is 90%
This is true. N-demethylation of ketamine occurs in the liver. The metabolite, norketamine which has significantly less activity than its parent compound is excreted in the urine after conjugation to water-soluble glucuronide derivatives. While a small percentage of ketamine is excreted unchanged in the urine, administration of this drug is not recommended in patients with cirrhosis.


B. High lipid solubility

This is true. Ketamine’s high lipid solubility confers easy passage through the blood brain barrier. Additionally, this together with ketamine’s low protein binding facilitates a large volume of distribution (3-5L/kg).

C. Elimination half life of 2-3 hours

This is true. After IV administration, ketamine’s effect is notable in 1-2 minutes, then rapidly distributed as reflected by a brief distribution half life (10-15 min). Clearance of this drug is high as reflected by its relatively short elimination half life (2-3 hours).

D. The bioavailability of the Intranasal route is 90%

This is not true. The bioavailability of the intranasal (IN) route is 50%. While IN is not FDA-approved, evidence of its analgesic effect in a placebo-controlled study of 40 patients is notable. Pain relief was achieved after 50 mg IN in patients undergoing third molar extraction.

Intranasal ketamine is the most common route for recreational use. Onset of feeling ‘high’ (enhanced sensory perception, out-of-body experiences and visual hallucinations) is in 5-10 minutes and lasts just over an hour.